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(54) Title: TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST		
(57) Abstract <p>A topical opioid paradigm was developed to determine analgesic peripheral effects of morphine. Topical morphine as well as peptides such as [D-Ala²,MePhe⁴,Gly(ol)⁵]enkephalin (DAMGO) produced a potent, dose-dependent analgesia using the radiant heat tailflick assay. The topical drugs potentiated systemic agents, similar to the previously established synergy between peripheral and central sites of action. Local tolerance was rapidly produced by repeated daily topical exposure to morphine. Topical morphine tolerance was effectively blocked by the N-Methyl-D-Aspartate (NMDA) receptors antagonist MK801 and ketamine given either systemically or topically. NMDA receptor antagonists reversed pre-existing morphine tolerance. The activity of topical NMDA antagonists to block local morphine tolerance suggests that peripheral NMDA receptors mediate topical morphine tolerance. Morphine was cross tolerant to [D-Ala²,MePhe⁴,Gly(ol)⁵]enkephalin (DAMGO), but not to morphine-6β-glucuronide, implying different mechanisms of action. These observations have great importance in the design and use of opioids clinically. Topical pharmaceutical compositions comprising an analgesic that functions through an opiate receptor and an NMDA receptor antagonist for producing analgesia without inducing tolerance are described.</p>		